

## [Correspondence] Clonal hematopoiesis and atherosclerosis

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**Table 1. Characteristics of the 103 Infants Who Underwent MRI.\***

Characteristic	Value
Female sex — no. (%)	57 (55)
Age at MRI — days	
Median (IQR)	61 (43–95)
Range	30–173
Gestational age at onset of maternal infection	
Median (IQR) — wk	24 (12–32)
Range — no. (%)	
>4 to 13 wk	31 (30)
>13 to 26 wk	25 (24)
>26 wk	47 (45)
Gestational age at birth — wk	
Median (IQR)	39 (38–40)
Range	33–41

\* IQR denotes interquartile range, and MRI magnetic resonance imaging.

(ventricular asymmetry) that were thought to be unrelated to ZIKV infection.

Our findings suggest that prenatal ultrasonography in ZIKV-infected pregnant women can detect ZIKV-associated morphologic changes in the fetus and thus may inform decision making among such women who may be considering

pregnancy termination.<sup>5</sup> Long-term functional outcome studies correlated to imaging findings are warranted.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

1. Boeuf P, Drummer HE, Richards JS, Scoullar MJ, Beeson JG. The global threat of Zika virus to pregnancy: epidemiology, clinical perspectives, mechanisms, and impact. *BMC Med* 2016; 14:112.

2. Cauchemez S, Besnard M, Bompard P, et al. Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *Lancet* 2016;387:2125–32.

3. Brasil P, Pereira JP Jr, Moreira ME, et al. Zika virus infection in pregnant women in Rio de Janeiro. *N Engl J Med* 2016;375: 2321–34.

4. Soares de Oliveira-Szeinfeld P, Levine D, Melo AS, et al. Congenital brain abnormalities and Zika virus: what the radiologist can expect to see prenatally and postnatally. *Radiology* 2016; 281:203–18.

5. Aiken A, Aiken CE, Trussell J. In the midst of Zika pregnancy advisories, termination of pregnancy is the elephant in the room. *BJOG* 2017;124:546–8.

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## Clonal Hematopoiesis and Atherosclerosis

**TO THE EDITOR:** Jaiswal and colleagues (July 13 issue)<sup>1</sup> report that the presence of clonal hematopoiesis of indeterminate potential (CHIP) was associated with coronary heart disease. However, the use of the JAK2 V617F mutation as a marker of CHIP may be misleading, particularly when the mutant allele burden is high (up to 52% in this study). Unlike all the other mutations that were evaluated by the authors, JAK2 V617F is an initiating mutation that causes deregulated production of red cells and platelets.<sup>2</sup> It is a major criterion in the classification of the World Health Organization (WHO) for a diagnosis of myeloproliferative neoplasms, diseases that are often diagnosed after major thrombosis, including myocardial infarctions.<sup>3–5</sup> Jaiswal and colleagues considered that leukocyte counts can be used to rule out myeloproliferative neoplasms, whereas

hematocrit and platelet counts are much more relevant for this purpose, especially in polycythemia vera and essential thrombocythemia. In the absence of full blood counts, one could speculate that many of the patients with a high JAK2 V617F allele burden are more likely to have undiagnosed myeloproliferative neoplasms than to be healthy CHIP carriers. Therefore, we suggest that the JAK2 V617F mutation should not be included in the definition of CHIP because of its specific involvement in the pathogenesis of myeloproliferative neoplasms.

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No potential conflict of interest relevant to this letter was reported.

1. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med* 2017;377:111-21.
2. Spivak JL. Myeloproliferative neoplasms. *N Engl J Med* 2017;376:2168-81.
3. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood* 2016;127:2391-405.
4. Tefferi A, Pardanani A. Myeloproliferative neoplasms: a contemporary review. *JAMA Oncol* 2015;1:97-105.
5. Kiladjian JJ, Giraudier S, Cassinat B. Interferon-alpha for the therapy of myeloproliferative neoplasms: targeting the malignant clone. *Leukemia* 2016;30:776-81.

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**TO THE EDITOR:** Jaiswal et al. report the results of four case-control studies that confirm a near doubling in the risk of coronary heart disease in patients with CHIP,<sup>1</sup> a finding that was first reported in the *Journal* in 2014.<sup>2</sup> The authors postulate that two mechanisms may be involved: the promotion of inflammatory responses, as supported in a study involving *Tet2* knockout mice, and an increase in the number of myeloid cells, a finding that appears to be more relevant for patients with *JAK2* mutations, which confer a much larger risk than the more common *DNMT3A*, *TET2*, and *ASXL1* mutations, in which blood counts remain normal.

However, the authors do not provide data relating to red-cell distribution width, which is the only blood-cell index that has been shown to have a significant association with CHIP<sup>2</sup> and which has been associated with an unexplained increase in all-cause mortality in an aging population.<sup>3,4</sup> In understanding how CHIP promotes atherosclerosis, it is important to explore the causal relationship between clonal hematopoiesis and red-cell anisocytosis to determine whether these are independent or associated risk factors for cardiovascular disease.

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No potential conflict of interest relevant to this letter was reported.

1. Keaney JF Jr. CHIP-ping away at atherosclerosis. *N Engl J Med* 2017;377:184-5.
2. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014;371:2488-98.
3. Patel KV, Ferrucci L, Ershler WB, Longo DL, Guralnik JM. Red blood cell distribution width and the risk of death in middle-aged and older adults. *Arch Intern Med* 2009;169:515-23.
4. Perlstein TS, Weuve J, Pfeffer MA, Beckman JA. Red blood cell distribution width and mortality risk in a community-based prospective cohort. *Arch Intern Med* 2009;169:588-94.

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**THE AUTHORS REPLY:** Cassinat et al. correctly state that patients with myeloproliferative neoplasms have an elevated risk of thrombosis, which several studies have concluded is related to the degree of leukocytosis but not thrombocytosis or erythrocytosis.<sup>1-3</sup> In our previous study, five of the six patients with *JAK2*-mutated CHIP did not have any abnormalities in the complete blood count and thus would not have met the WHO criteria for either polycythemia vera or essential thrombocythemia.<sup>4</sup> In the current study, data regarding the complete blood count were available for patients from the Malmö Diet and Cancer prospective cohort study. Of the two patients with *JAK2* mutations in that cohort, one had no blood-count abnormalities and the other had mild thrombocytosis (463,000 platelets per microliter). It is possible that clinically evident myeloproliferative neoplasms will be diagnosed in some, or even most, of these patients after several years. However, we believe it is premature to conclude that *JAK2* V617F should not be included in the definition of CHIP on the basis of current information.

Phillips et al. suggest that increased red-cell anisocytosis may be associated with both CHIP and atherosclerotic cardiovascular disease, thereby pointing to the causal biologic features that link these phenomena. Data on red-cell distribution width-standard deviation (RDW-SD) were available from the complete blood count in patients in the Malmö Diet and Cancer cohort. In this relatively small sample, CHIP was not significantly associated with the RDW-SD. The presence of CHIP was associated with an increase in the RDW-SD of 1.85 fl ( $P=0.32$ ), after adjustment for age, sex, coronary heart disease status, type 2 diabetes status, and smoking history. The inclu-

sion of the RDW-SD in a Cox proportional-hazards model for the development of coronary heart disease did not affect the risk estimate associated with CHIP (hazard ratio, 1.99; 95% confidence interval, 1.26 to 3.13), after adjustment for RDW-SD, age, sex, hypertension, type 2 diabetes status, smoking history, and levels of high-density lipoprotein cholesterol and total cholesterol. On the basis of this limited sample, we found no evidence that red-cell anisocytosis, as indicated by an elevated RDW-SD, mediates the association between CHIP and atherosclerotic cardiovascular disease.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Campbell PJ, MacLean C, Beer PA, et al. Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. *Blood* 2012;120:1409-11.
2. Carobbio A, Finazzi G, Guerini V, et al. Leukocytosis is a risk factor for thrombosis in essential thrombocythemia: interaction with treatment, standard risk factors, and Jak2 mutation status. *Blood* 2007;109:2310-3.
3. Landolfi R, Di Gennaro L, Barbui T, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. *Blood* 2007;109:2446-52.
4. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014;371:2488-98.

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## Itraconazole or Amphotericin B for Talaromycosis

**TO THE EDITOR:** Le et al. (June 15 issue)<sup>1</sup> report that amphotericin B was superior to itraconazole in the treatment of talaromycosis and that the rates of adverse events were higher with amphotericin B use. However, some issues need to be discussed. The investigators did not report severity of illness or preexisting medical conditions. The treatment of talaromycosis depends on the severity of the infection, because itraconazole is recommended for milder forms of talaromycosis and amphotericin B or voriconazole for more severe forms.<sup>2</sup> The efficacy of treatment in both study groups can be misleading if, for instance, patients were not adequately treated or were overtreated on the basis of the severity of their infection. The presence of preexisting medical conditions could influence treatment outcomes, because patients with these conditions may be more susceptible to negative outcomes.

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No potential conflict of interest relevant to this letter was reported.

1. Le T, Kinh NV, Cuc NTK, et al. A trial of itraconazole or amphotericin B for HIV-associated talaromycosis. *N Engl J Med* 2017;376:2329-40.
2. Spanakis EK, Aperis G, Mylonakis E. New agents for the treatment of fungal infections: clinical efficacy and gaps in coverage. *Clin Infect Dis* 2006;43:1060-8.

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**TO THE EDITOR:** Le et al. compared the efficacy of amphotericin B, administered intravenously, with that of itraconazole, administered orally, in the treatment of talaromycosis and found that amphotericin B was superior. The survival benefit was thought to be associated with greater fungicidal activity of amphotericin B, but the authors did not take into account the highly variable absorption kinetics of itraconazole capsules. Itraconazole is a weakly basic drug, and dissolution of the drug is pH-dependent; thus the drug requires an acidic gastric environment for adequate absorption.<sup>1</sup> Numerous studies have documented substantial variation in itraconazole exposure owing to the effect of food, interaction with co-administered drugs, and adherence.<sup>2</sup> Guidelines recommend assessment of the exposure to itraconazole through therapeutic drug monitoring when the drug is used for treatment of systemic